NOV 27 2006

This report is required by law (7 USC 2143) Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150

See reverse side for additional information

Interagency Report Control No 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. REGISTRATION NO. 51-F-0003 / 443

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

2. HEADQUARTERS RESEARCH FACILITY (Name and Address, as registered with USDA include Zip Code)

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTES
AFRRI/VSD
8901 WISCONSIN AVENUE
BETHESDA, MD 20889

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)

FACILITY LOCATIONS (Sites)

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS FORM 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used	E. Number of animals upon which teaching experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress in those animals and the reasons such drugs were not used must be attached to this report)*	F. TOTAL NO. OF ANIMALS (Cols. C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs					
7. Hamsters					
8. Rabbits					
9. Non-human Primates			51		51
10. Sheep					
11. Pigs					
12. Other Farm Animals					
Mice	1,467	2,159	1,777	11,366	15,302
13 Other Animals					

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). A summary of all such exceptions is attached to this annual report. In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)
I certify that the above is true, correct, and complete (7 U.S.C. Section 2143).

(b)(6), (b)(7)(c)

DATE SIGNED
11/21/06

(AUG 91)

Category E justifications

Protocol 1 10 mice

Pain and distress in 10 mice were produced from ionizing radiation. These could not be relieved because pain relievers are known to interfere with the body's normal biological response to radiation and would thus confound the study. It is necessary to study the effects of ionizing radiation under those conditions that would occur in a military field of operations.

Protocol 2 252 mice

Radiation-induced injuries do cause some pain and/or distress in animals. We do not use drugs to control this pain as such drugs could alter the outcome of the experiments. Animals determined to be demonstrating acute morbidity are euthanized.

Protocol 3 280 mice

Since the purpose of these studies is to determine the effects of radiation and radioprotectants on the functions of the immune and blood-forming systems, we will be unable to use analgesics and anesthetics since they have effects on immune system function (altered cytokine expression) that would interfere with the interpretation of our results

Protocol 4 435 mice

There are no alternative procedures for irradiation because it is a unique stimulus that cannot be otherwise duplicated. Radiation itself does not cause pain or distress. In fact, radiation can alleviate the pain associated with cancer (Bateman, 1994; Ciezki and Macklis, 1995; Page, 1995; Sonoo et al., 1995; Thrall, 1995). Nevertheless, the sequelae of nausea, vomiting, and diarrhea cause pain and distress in humans in the early post-irradiation period, when lethal doses are used. However, mice are not susceptible to vomiting. Although radiation does not induce pain, animals in these experiments might experience pain and distress prior to death because of sequelae. To avoid possibly affecting survival/death outcomes, and ultimately LD50/30 and LD95/30 calculations, analgesics/sedatives will not be administered after challenge so as not to interfere with the clinical course of the disease. The attending veterinarian was consulted with respect to the procedures described above, when they were used on previous protocols.

Bacteria cause infections that cause discomfort either locally or systemically. Many pathogenic bacteria have unusual or even unique virulent characteristics, but they also have common attributes, including binary multiplication and penetration of tissues, and cause common responses and disease processes in animals, which cannot be mimicked readily by substitutes. Although, by necessity, there are animals included in the unalleviated pain-and-distress category in this protocol, there will be a conscious effort by the P.I. and animal care staff to provide as much additional consideration for the comfort and well-being of the animals as is consistent with the scientific integrity of the study. These studies are designed to assess the susceptibility and immune response to the combined effects of ionizing radiation and bacterial infection. There are no alternatives to the use of animals in these studies. Similarly, there are no alternatives to bacterial challenge or natural, radiation-induced infection, because protective immunity cannot be predicted from seroconversion alone at this time when it occurs. Moribund animals will be euthanized as indicated below to alleviate further pain and distress.

Although we expect that test therapeutic agents will provide some relief to some of the mice, an alternative for these procedures would be to determine whether an analgesic could be used to relieve pain and discomfort. Although the opioid analgesics, butorphanol and bupenorphine, might be used to alleviate local pain associated with a local infection without altering the local inflammatory response (Swearengen et al. 1993), opioid analgesics are immunomodulatory (Pruett et al. 1992, Pasotti et al. 1993, Carr et al. 1994). Other, non-narcotic analgesics, such as indomethacin, are anti-inflammatory, so they would interfere with the inflammatory responses of the hemopoietic tissues to infections. Analgesics cause adverse effects on undamaged hematopoietic cells (Hollaender, 1960) and interfere with nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, a key polymorphonuclear leukocyte enzyme that is involved in the ability of these cells to phagocytize and kill bacteria (Moon et al., 1986).

REFERENCES (Painful Procedure Justification):

Bateman, K.E. 1994. 0-7-21 radiation therapy for the palliation of advanced cancer in dogs. J. vet. intern. med. 8: 394-399.

Carr, D. J., Gerak, L. R., and France, C. P. 1994. Maltrexone antagonizes the analgesic and immunosuppressive effects of morphine in mice. J. Pharmacol. Exp. Ther. 269(2):693-698.

Ciezki, J., and Macklis, R. M. 1995. The palliative role of radiotherapy in the management of the cancer patient. Semin. Oncol. 22(2, Suppl 3):82-90.

Hollaender, A., ed. 1960. Radiation protection and recovery. Pergamon Press, London.

Moon, B. C., M. J. Girotti, S. G. F. Wren, R. Dawson, and D. Brar. 1986. Effect of antibiotics and sedatives on normal neutrophil nicotinamide adenine dinucleotide phosphate-reduced oxidase activity. Arch. Surg. 121:73-76.

Page, R. L. 1995. Radiation therapy in the management of pain associated with cancer. Proc. North Am. Vet. Conf. Jan. 14-19, 1995, Orlando, Florida. p. 258.

Pasotti, D., Mazzone, A., Lecchini, S., Frigo, G. M., and Ricevuti, G. 1993. Influenza dei peptidi oppioidi sui granulociti del sangue periferico. [The effect of opioid peptides on peripheral blood granulocytes.] Riv. Eur. Sci. Med. Farmacol. 15(2):71-81.

Pruett, S. B., Han, Y. C., and Fuchs, B. A. 1992. Morphine suppresses primary humoral immune responses by a predominantly indirect mechanism. J. Pharmacol. Exp. Ther. 262(3):923-928.

Sonoo, H., Shimozuma, K., Kurebayashi, J., Ohta, K., and Kiyono, T. 1995. [Systemic therapy, pain relief and quality of life of breast cancer patients with bone metastasis.] Gan To Kagaku Ryoho 22 Suppl 1:10-15.

Swearengen, J. R., Cockman-Thomas R. A., Davis, J. A., and P. J. Weiss. 1993. Evaluation of butophanol tartrate and bupenorphine hydrochloride on the inflammatory reaction of the Sereny Test. Lab. Animal Sci. 43(5):417-525.

Thrall, D.E. 1995. Palliative radiation therapy. Sem. vet. med. surg. (small anim.) (special issue on Radiation oncology edited by E. L. Gillette)10:205-208.

Protocol 5 1152 mice

Radiation exposure results in various metabolic changes including loss of blood elements such as neutrophil. This may result in opportunistic infection and pain associated with such an infection. Since the purpose of these studies is to determine the effects of radiation and radioprotectants on the functions of the immune and blood-forming systems, we will be unable to use analgesics and anesthetics since they have been shown to have direct effects on immune system function and hence would interfere with the interpretation of our results.

Protocol 6 1919 mice

Exposure to different doses of radiation produces biologic effects, which may not be causing immediate pain, but can result in painful sequelae. In order to obtain results purely due to the potential radioprotectant under study, it is important not to treat the animals with analgesics or antipyretics. It has been reported that some of these agents interfere with hematological responses of the treated animals. Since hematological responses are also one of the main targets of radiation, treatment with agents other than the radioprotectant under study might lead to erroneous conclusions about the efficacy of the radioprotectant. The resulting uncertainty in the studies may necessitate repetition of the experiments that require additional animals.

Protocol 7 2356 mice

Exposing animals to radiation may cause distress in mice but at present there are no in vitro models to predict radiation protection. In mice, (Teskey, GC et al. Life Sci., 35, 1547,1984) and humans (Wu,JS. et al. Clin Oncol (R Coll Radiol). 18,:539, 2006), radiation has been reported to reduce pain and distress. Due to preclinical testing requirements mandated by the FDA, the development of new radiation countermeasure drugs destined for human use must be investigated in a rodent model, since it would be unethical to irradiate healthy humans.

Protocol 8 4,962 mice

The use sedatives and analgesics will be used with a degree of caution and on an individual animal-in-need basis. Reasons for our proposed limited use of sedatives and analgesics only in cases of severe pain/discomfort are as follows: (1) in mice, clinical signs of minimal or even moderate pain/discomfort have the potential to interfere with the identification of clinical signs and alter the hematological and survival responses of the treated animals, and (b) the use and analgesics and anesthetics on an individual basis might interfere with basic functional elements of the irradiated animal's innate and acquired immune system. In this regard for example, there is a wealth of information that clearly documents the effect of sedatives and opiates on neutrophil production and function.